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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,630	02/26/2002	Claudia Ulbrich	P67344US0	1109

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,630	ULBRICH ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *17-24,27-30 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *17-24,27-30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/11/02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 20 and 24 have been amended. Claim 31 has been canceled. Claim 32 has been added. Claims 17-24, 27-30 and 32 are pending and under consideration.

2. Sections of Title 35, U.S. Code, not found in this action can be found in a prior action.

3. The rejection of claims 17-24 and 27-30 under 35 U.S.C. 103(a) as being unpatentable over Holtl et al (Journal of Urology, March 1999, Vol. 161, pp. 777-782, cited in a previous action) in view of Grossmann et al (Anticancer Research, 1997, Vol. 17, pp. 3117-3120, reference of the IDS filed January 11, 2002) is maintained for reasons of record. Claim 32 is rejected for the same reasons of record

Claim 17 is drawn to a composition obtainable by a process in which tumor material is evaluated, comminuted and made into a purified cell suspension, which is then incubated with IFN-gamma and tocopherol acetate and frozen to from a tumor cell lysate, and in which monocytes are isolated from buffy coats or whole blood and subsequently induced to differentiate into dendritic cells by incubation with cytokines and converted to the non-adherent stage, whereupon tumor cell lysate is thawed and said thawed lysate and cytokines are added to the non-adherent dendritic cells, followed by incubation of the admixture and harvesting of the mature dendritic cells. Claim 18 embodies the composition of claim 17, wherein Il-4 and GM-CSF are added for differentiation into immature dendritic cells.

Claim 19 is drawn to a medicament containing the composition according to claim 17 in combination with an acceptable carrier.

Claim 20 is drawn to a method for preparing a medicament in which a suspension of tumor cells is prepared, which is then incubated with IFN-gamma and tocopherol acetate, the tumor cells are killed, and monocytes are isolated from blood, their differentiation into dendritic cells is induced and the thus obtained immature dendritic cells are incubated with the cell lysate of the killed tumor cells, the maturing of the dendritic cells is induces and the mature dendritic cells are harvested as the medicament. Claim 21 embodies the method of claim 20 wherein the

monocytes are isolated from buffy coats, whole blood, leukapheresis, or separated stem cells. Claim 22 embodies the method of claim 20 wherein the differentiation of the monocytes into immature dendritic cells is induced by cytokines, Il-4 and GM-CSF with or without IFN-gamma. Claim 23 embodies the method of claim 20 wherein the dendritic cells are matured from immature DC to mature DC by prostaglandin E2 and TNF-alpha and/or Il-1beta and Il-6 in addition to Il-4 and GM-CSF. Claim 24 embodies the method of claim 20 wherein the tumor cell suspension is prepared by isolated and optionally evaluating tumor material, which is then comminuted and made into a purified cell suspension. Claim 27 embodies the method of claim 20 wherein the tumor cells are killed by freezing. Claim 28 embodies the method of claim 20 wherein the mature DC are harvested when typical morphological characteristic of cell maturity are present as evaluated by microscopic check and/or by characterization of surface antigens using fluorescent antibodies. Claim 32 embodies the method of claim 20 wherein the tumor cell suspension is prepared by isolating and evaluating tumor material which is then comminuted into a purified cell suspension.

Claim 29 is drawn to a method of using the composition of claim 17 for tumor therapy comprising administering the composition to a patient. Claim 30 embodies the method of claim 29 wherein the tumor material is autologous.

Holtl et al teach a method of making a therapeutic composition by the method comprising culturing human dendritic cells from buffy coats with the cytokines Il-4 and GM-CSF (page 778, under the heading "Culture of dendritic cells") which fulfills the specific requirements of claims 18, 21 and 22); preparation of a tumor cell lysate from autologous tumor cells which have been minced, digested with collagenase and deoxyribonuclease, washed and plated in 96-well plates in order to eliminate non-adherent cells and lysed under hypotonic conditions (page 779, under the heading "Preparation of tumor cell lysates") which fulfills the specific embodiment of claim 30. Holtl et al teach that the autologous tumor cell lysate was added to the cultured dendritic cells with TNF-alpha and prostaglandin E2 (page 779, under the heading of "Pulsing of dendritic cells") which fulfills the specific requirement of claim 23. Holtl et al teach that the phenotype of the dendritic cells was determined by using fluorescent labeled antibodies to determine the presence of HLA-ABC, HLA-DR, CD 83 and CD86 (page 778, second column, lines 3-9) which fulfills the specific embodiment of claim 28. Holtl et al teach that the pulsed dendritic cells were

suspended in lactated Ringer's solution with 1% autologous serum for subsequent bolus infusion (page 779, second column, lines 1-3) which fulfills the specific embodiment of an "acceptable carrier" in claim 19. Holtl et al do not teach a tumor cell lysate which was incubated with IFN-gamma and tocopherol acetate, wherein the tumor cells were then killed by freezing.

Grosmann et al teach a composition comprising human pancreatic carcinoma taken from patients, wherein the tumor tissue was mechanically disassociated, and the resulting tumor cells were checked for viability using trypan blue (page 3117, first paragraph under "Materials and Methods"). Grosmann et al teach that said disassociated cells were incubated with IFN-gamma and tocopherol acetate and subsequently frozen to render devitalized tumor cells (page 3117, second paragraph under "Materials and Methods"). Grosmann et al teach that incubation of the tumor cells with IFN-gamma and tocopherol acetate led to an increase in the amount of MHC I presentation and that this increase leads to a more efficient recognition by immunocompetent cells and an increase in recruitment of cytotoxic T-lymphocytes (page 3118, second column, lines 5-9 and page 3119, lines 1-5). Grosmann et al suggest that pancreatic carcinoma cells prepared as described can be used in immunotherapy similarly to renal cell carcinoma, malignant melanoma and colon carcinoma (page 3119, last sentence).

It would have been prima facie obvious at the time the claimed invention was made to substitute the specific composition obtainable by the method Grosmann et al as the autologous tumor cells taught by Holtl et al for a method of treating pancreatic carcinoma. One of skill in the art would have been motivated to do so by the suggestion of Grosmann et al that human pancreatic tumor cells treated with IFN-gamma and tocopherol acetate express increased amounts of MHC I and thereby can be effectively recognized by immunocompetent cells and therefore function in immunotherapy in the same manner as renal cell carcinoma, malignant melanoma and colon carcinoma. It is noted that the check for viability carried out by Grossman et al fulfills the embodiment of evaluating tumor material before the cell suspension is made.

4. Applicant argues that the salient feature of the invention is the use of a cell suspension having fragments of the tumor cell and that this embodiment is not taught by the cited references. this has been considered but not found persuasive. It is noted that the requirement for a cell suspension having pieces of tumor membrane is not part of the claim limitations. The claims

require the use of a "crude lysate" which can be satisfied by the use of any cell lysate that is a mixture versus a pure substance.

5. Applicant argues that Holtl teaches away from the claimed invention because Holtl uses centrifugation to clear the lysates. This has been considered but not found persuasive. Applicant presents no arguments or evidence that the same tumor cell antigens found on the tumor cell membrane would not be available in the cell lysate of Holtl et al. It is well known in the art that tumor cell antigens are expressed in the context of MHC I on the cell surface, but the aforesaid antigens are first translated within the ribozymes and then to some degree taken up in endogenous peptide processing for MHC class I presentation. Thus, a crude lysate absent solid membrane fragments would possess the spectrum of antigens which would be the precursors of the antigens to be presented in MHC I.

6. All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicant's amendments.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
5/29/2006